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08/304,147	09/12/94	ROBERTS L	9101BCIP

EXAMINER	
ART UNIT	PAPER NUMBER
1811	12

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DATE MAILED: 01/21/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10/28/96 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), -0- days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 4-7 and 9-20 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 2-3 and 8 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1, 4-7 and 9-20 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The communication filed 10/28/96 is acknowledged. In view of Applicants request claims 2-3 and 8 have been canceled, claims 10-20 have been added. Thus, claims 1, 4-7 and 9-20 are now pending in the application.

The rejection under 35 USC 103 over the prior art of record is maintained.

Applicant's arguments filed 10/28/96 have been fully considered but they are not deemed to be persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 4-7 and 9-20 are rejected under 35 USC 103 as being unpatentable over Morrow et al., (Analytical Biochemistry, Volume 184, pp. 1-10, January 1990).

The rejection under 35 USC 103 for claims 1, 4-7, 9 and newly submitted claims 10-20 over the prior art of record is maintained essentially for the reasons discussed on the previous Office action. With respect to Applicants allegation that the reference of Morrow et al. does not teach any of the details of the present invention, particularly in terms of the specifics of

the storage and preparation of samples, that are necessary in order to prevent further oxidation of prostaglandin F_2 and other eicosanoids in vitro. Therefore, the use of the assay described in Marrow et al. would lead to inaccurate measurements of the oxidation products of these compounds, resulting in an erroneous and, thus, useless assay for determining oxidative stress in vivo is not persuasive. Although, Applicants have amended the claims to include the limitations of in vivo assay on fresh samples within about two hours, processing the samples at -70°C, and adding antioxidants to or partially processing the samples to allow storage at -20°C. However, contrary to Applicants allegation, it is the Examiner's position that as acknowledged on pages 8-9 of Applicants Remarks filed 10/28/96 that Morrow et al. disclose the discovery that several prostaglandin F_2-like (PGF_2) compounds can be found in the plasma from normal volunteers that were believed to be derived from prostaglandin D_2 are actually formed by non-enzymatic, chemical oxidation mechanisms upon the storage of plasma samples. This finding has significant implications for the accuracy of the measurement of prostaglandin F_2 and other eicosanoids in plasma samples. This reference also discloses an assay system that detects prostaglandin F_2 compounds and their prostanoid metabolites, at levels ranging from approximately 5 to 40 picograms per millimeter using gas chromatography negative ion chemical ionization mass

spectroscopy. Thus, clearly showing the methods of determining the oxidative stress in vitro.

The Examiner acknowledge's the prior art of Morrow et al. does not teach a method of determining the oxidative stress in vivo. However, it would be obvious to select and use any known method of interest for the intended purpose of determining oxidative stress in vivo. Based on in vitro experimentation (investigative data), one of ordinary skill in the art would develop an art recognized animal model and correlate to human utility for potential therapeutic agent which eventually intended for human application. Therefore, one of ordinary skill in the art would have been motivated to develop or use the already established in vitro data of Morrow et al. for the in vivo efficacy of the instantly claimed invention.

Moreover, the instant method, which falls within the scope of the prior art method and composition would have been prima facie obvious from said prior art disclosure to a person of ordinary skill in the art at the time the invention was made because in the absence of sufficient evidence to the contrary, Applicants claims are directed to optimization of an "art recognized variable" which is well within the purview of one of ordinary skill in the art In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). Also, the selection of the appropriate prostanoids, comparing the said prostanoids with a control and

determining oxidative stress on said comparison is conventional and within the skill of the art to which this invention pertains.

Thus, Applicants allegation that the use of the assay described in Marrow et al. would lead to inaccurate measurements of the oxidative products of these compounds, resulting in an erroneous, and, thus useless assay for detecting oxidative stress in vivo is not persuasive, absent of showing a side by side comparison to validate the allegation. However, Applicants are cautioned that this is not an invitation to prolong the prosecution of after Final rejection.

Applicants have argued that the specifics of the in vitro assay methods and parameters in the instant invention, particularly in terms of the specifics of the storage and preparation of samples, do not overlap those of the in vivo assay, and, in fact, are very different from them. Specifically, the necessity of performing the in vivo assay on fresh samples within about two hours, storing the samples at -70°C, adding antioxidants to or partially processing the samples to allow storage at -20°C, and having to treat different biological samples differently are, in fact, not predictable from the in vitro assay and, therefore, they are unexpected results, thus rebutting the assertion of prima facie obviousness. It is the Examiner's position again that the prior art clearly teaches on page 1, the specifics of storing the samples at -20°C, on page 5,

the addition of antioxidants, and on page 6, performing the in vitro assay within 4 hours. Thus, the instantly claimed method and composition falls within the scope of the prior art method and composition and as such it would have been obvious for one of ordinary skill in the art to modify or optimize the "in vitro assay" since the general conditions of the claimed method and composition are disclosed in the prior art. Further, Applicants have acknowledged on page 2 of the Remarks (See the preliminary amendment filed 12/5/94) that the prior art teachings of in vitro has fulfilled a great need in the art which lead to the development of an assay to determine oxidative stress in vivo by the quantification of these prostaglandin compounds. Thus, one of ordinary skill in the art would have been motivated to correlate the in vitro data to potential animal model in order to determine the in vivo efficacy because, a person of ordinary skill in the art would know that a **first line** of experimentation is the in vitro experimentation.

Applicants have also argued that the rejection is based on the impermissible "obvious to try" standard. The impermissible obvious to try test is not applied here. Rather, in view of the implicit motivation of the analogous Morrow et al. in vitro data and as acknowledged by Applicants that the Morrow et al. reference lead to the Applicants investigating in this area further resulting in piquing Applicants curiosity (See page 29 of

the brief filed 11/30/93 as Paper No. 16 on parent application Serial No. 07/715,419); the reference taken as a whole would have suggested Applicants invention of a method of determining oxidative stress in vivo by quantification of prostaglandin-like compounds and their metabolites produced by a noncyclooxygenase free radical catalyzed mechanism in either biological fluid or tissue and a composition thereof to one of ordinary skill in the art. Furthermore, obviousness does not require absolute predictability, In re Lamberti, 192 USPQ 278; In re Migel et al, 159 USPQ 716; In re Moreton, 129 USPQ 288 but only reasonable expectation of success, In re Longi, 225 USPQ 645; In re Pantzer et al, 144 USPQ 415; In re Farnham et al, 188 USPQ 365.

Accordingly, it would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the teachings of Morrow et al., thus achieving the invention as a whole for the expected benefits of employing a method to determine oxidative stress in vivo by quantification of prostaglandin-like compounds and their metabolites produced by a noncyclooxygenase free radical catalyzed mechanism; absent of sufficient objective factual evidence or unexpected results to the contrary.

No claim is allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 6:30 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on (703) 308-0254. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

C Tsang

CECILIA J. TSANG
SUPERVISORY PATENT EXAMINER
GROUP 1800

AAM Mohamed/AAM
January 13, 1997